New Cell Lines

I. Purpose

The CIRM New Cell Lines Awards will support the derivation and propagation of new lines of pluripotent human stem cells that will have important research and clinical application for understanding, diagnosing and treating serious injury and disease. CIRM intends to provide funding for qualified investigators to conduct research in California that will lead to the generation of new human embryonic stem cell lines and/or to the optimization of new, alternate methods for the derivation of pluripotent human cell lines.

II. Program Objectives

Pluripotency is defined as the ability to differentiate into cell types representing all three germ layers – ectoderm, mesoderm and endoderm. Pluripotent stem cells have the potential to play a key role in regenerative medicine and in cell replacement therapies because of their unique ability to self-renew and their developmental potential to form all cell lineages in the body.

Pluripotent human stem cells have been successfully generated from early stage human embryos (human embryonic stem cells, hESC) and from the fetal gonadal ridge (human embryonic germ cells). The most common technique for deriving hESC involves the utilization of excess blastocysts from *in vitro* fertilization, although other sources of early stage human embryos, such as those rejected after preimplantation genetic diagnosis or those generated following parthenogenetic activation of oocytes, are currently being explored. Alternative methods for producing pluripotent stem cells such as reprogramming of adult somatic cells or their nuclei are also being pursued. Somatic cell nuclear transfer (SCNT), a method for reprogramming that is well-established in several mammalian species, has not yet been achieved with human cells, but recent success has been reported in non-human primates. In another recent breakthrough, reprogramming of somatic cells to a pluripotent state by retrovirus-mediated over-expression of specific transcription factors (induced pluripotent stem cells, iPS cells) has been accomplished using human fetal and adult cells. Finally, numerous efforts have been launched to find, document, and verify the presence of pluripotent stem cells in adult tissues. New technologies are thus being developed to enable the generation of human pluripotent stem cells from a variety of embryonic and adult sources.

Embryonic sources currently provide the only means of producing human pluripotent stem cells that are genetically unmodified. Therefore, derivation of new hESC lines is a priority for both basic and translational research. On the other hand, the genetic background of human pluripotent stem cell lines is determined by the donors of the material used for their generation, which, in the case of hESCs, is at present limited mainly to excess or rejected embryos from *in vitro* fertilization.

In order to develop cellular models of heritable disease, it is necessary to derive new cell lines with the genetic makeup that predisposes or leads to disease. Furthermore, a collection of new cell lines representing diverse genetic backgrounds may be an important tool for understanding the variation in responses to drugs by different patients. The generation of disease-specific or otherwise genotypically diverse human pluripotent stem cell lines that can differentiate into many cell types will have great value for drug discovery and toxicology testing. Finally, in preparation for cell-based therapies, new technologies for the generation of stem cell lines that are histocompatible with or specific to individual patients will provide a strategy to overcome the challenge of immune rejection. These needs may in the future be met by derivation of hESC following SCNT or by generation of iPS cells, two approaches that have seen important recent advances but are still very much in their infancy. Many hurdles need to be overcome before these methods are effective and safe enough to be considered for therapeutic applications.

CIRM proposes a new program to address the need for new types and sources of human pluripotent stem cell lines, and for the optimization of existing methods for their derivation. CIRM will fund research using well-established approaches based on early stage human embryos, as well as alternate methods that will enable greater genetic diversity and individualization of pluripotent stem cell lines. Importantly, methods that do not require the donation or use of either human embryos or eggs will reduce the ethical concerns that surround these approaches, and may help overcome the limitations inherent in obtaining excess embryos from diverse racial and ethnic groups.

This Request For Applications (RFA) will support the generation of a variety of new lines of pluripotent human stem cells such as (but not limited to):

- new clinical grade hESCs and other pluripotent human stem cell lines suitable for future clinical use or other biomedical applications
- new hESC lines that may be optimal for differentiation along selective lineages or for studies of disease
- disease-specific or otherwise genetically diverse, pluripotent stem cell lines to support studying the effects of genetic variation on disease mechanism and response to treatment, and the discovery and evaluation of new drug candidates
- the discovery and implementation of alternative methods for generating pluripotent human stem cells, including technology leading to the generation of patient-matched or disease-specific cell lines

In summary, the New Cell Lines Awards program of CIRM will encourage stem cell scientists in the state of California to develop and apply innovative approaches that will produce new and previously unavailable human pluripotent stem cell lines, some of which may be especially suited for therapeutic or specialized research applications. Because pluripotent stem cell lines may be derived from unexpected sources, CIRM will support a broad range of research using the full spectrum of human cell types and experimental approaches.

III. Award Information

CIRM New Cell Lines Awards will be offered to investigators with an MD, PhD or equivalent degree to conduct their research at an academic or non-profit research institution in California or at a for-profit organization with research sites located in California. The proposed research must be conducted within the state. **Awards will be made to support two categories of research:**

Category 1: Derivation of new hESC lines using excess or rejected early stage human embryos generated by *in vitro* fertilization.

Category 2: Derivation of pluripotent human stem cell lines from other sources using alternative methods such as (but not limited to) SCNT or reprogramming of neonatal or adult cells (iPS cells).

Particular consideration will be given to research applications that cannot be funded by current federal mechanisms.

Under this RFA, CIRM intends to commit up to $25 million to support up to 16 awards, eight (8) in each of the two categories of research. CIRM proposes to fund each award for up to three (3) years for direct project costs of up to $300,000 per year.

IV. Eligibility Information

Applications will only be accepted from Principal Investigators (PIs) who 1) have been officially nominated on a Candidate Nomination Form (CNF, see RFA section VI.A) by their host institution and 2) have submitted a Letter of Intent (LOI, see RFA section VI.B) that was accepted by CIRM.

A. Institutional Eligibility

All CIRM-supported research must be conducted in California. This RFA is open to all academic and Non-Profit research institutions in the state of California. It is also open to For -Profit organizations with research site(s) located in the state of California at the time the application is submitted. **Academic and Non -Profit applicant institutions are eligible to submit two applications in each research category (see section III of this RFA), for a total of up to four applications. For-Profit applicant institutions are eligible to submit one application in each research category (see section III of this RFA), for a total of up to two applications.**

Non-Profit organization means either: (1) a governmental entity of the state of California; or (2) a legal entity that is tax exempt under Internal Revenue Code section 501(c)(3) and California Revenue and Taxation Code section 23701d.

For-Profit organization means: an organization, institution, corporation, or other legal entity that is organized or operated for the profit or financial benefit of its shareholders or other owners. Such organizations also are referred to as “commercial organizations”.

B. Principal Investigator (PI) Eligibility

A Principal Investigator (PI) may submit only one application under this RFA. Candidates must have received an MD, PhD or equivalent degree and must be the individual who conducts or is responsible for the conduct of the proposed research on site at the applicant institution in California. PIs must devote a minimum of 10 percent effort exclusively to research proposed in their application.

V. Review Criteria

It is the intent of the New Cell Lines Awards to support the development of human stem cell lines that are pluripotent, *i.e.,* cell lines that can differentiate into derivatives of all three germ layers, the ectoderm, mesoderm, and endoderm. Applications will be evaluated in primarily two areas: the Significance and Innovation of the project, and the Design and Feasibility of the Research Plan.

1. **Significance and Innovation**

- The proposed methods or the cell lines that will be derived contribute to solving an important problem in stem cell biology.
- The proposed concept and approach are original and innovative.
- The proposed research, if successful, will significantly move the field forward, either scientifically or medically.

2. **Design and Feasibility of the Research Plan**

- The proposed research is carefully designed to give meaningful results.
- The rationale that derived cell lines will be pluripotent is convincing.
- The criteria used to confirm pluripotency of derived cell lines are sufficient.
- Potential difficulties are acknowledged, and alternative plans are provided should the proposed strategies fail.
- The preliminary data are compelling and supportive of the proposed concepts, hypotheses and approaches.
- The aims of the research can be reasonably achieved within the proposed timeframe.
- The PI and key personnel have the training and experience to conduct the proposed work.
- Evidence of prior success and track record supports the qualification of the PI to derive the new cell lines as proposed.

VI. Application Procedure

Applicant institutions and candidates must follow these instructions for submitting a Candidate Nomination Form, Letter of Intent, and Application for the CIRM New Cell Lines Awards. Applications will only be accepted from PIs who 1) have been officially nominated on a Candidate Nomination Form (CNF) by their host institution and 2) have submitted a Letter of Intent (LOI) that was accepted by CIRM.

A. Candidate Nomination Form (CNF)

Applicant institutions must submit to CIRM a single Candidate Nomination Form (CNF) using the CNF template provided at

https://www.cirm.ca.gov/grants/default.asp.The CNF must list the name, degree and employment title of each of the PIs the institution wishes to nominate for these awards. CIRM will accept only one CNF from each institution; this form must be signed by an institutional official authorized to nominate candidates on behalf of the entire institution. The signed original CNF must be received by CIRM no later than

5:00pm (PST) on January 10, 2008. No exceptions will be made.

Mail the signed original CNF to:

New Cell Lines Award Candidate Nomination Form

California Institute for Regenerative Medicine

210 King Street

San Francisco, CA 94107

B. Letter of Intent (LOI)

Each candidate nominated by their Institution must submit a letter of intent (LOI) using the LOI template provided at https://www.cirm.ca.gov/grants/default.asp. The letter should describe concisely the overall goals of the proposed research and technical approaches used to achieve these goals. Completed LOIs should be sent as an email attachment to NewCellLinesLOI@cirm.ca.gov, and must be received by CIRM no later than **5:00PM (PST) on January 10, 2008. Noexceptions will be made.** Letters of intent are non -binding, but applications will not be accepted if an LOI has not been received by CIRM by the stated LOI deadline.

C. Application Instructions

Application forms will be available online by December 17, 2007. The application for CIRM New Cell Lines Awards consists of three parts:

Part A: Application Information Form (Adobe PDF template provided at http://www.cirm.ca.gov/grants/default.asp.)

Part A includes: Abstract, Public Abstract, Statement of Benefit to California, Key Personnel, and Budget (section numbers 1, 2, 3, 11, and 12 below).

Part B: New Cell Lines Award Research Proposal (MS Word template provided at https://www.cirm.ca.gov/grants/default.asp.)

Part B includes: Rationale and Significance, Specific Aims and Timeline, Research Design and Methods, Preliminary Results and Feasibility, References, Collaborations and Plans for Sharing New Cell Lines, and Laboratory Facilities including major equipment (section numbers 4, 5, 6, 7, 8, 9, and 10 below).

Part C: Biographical Sketches for Key Personnel (MS Word template provided at https://www.cirm.ca.gov/grants/default.asp.) and letters of collaboration.

The application for New Cell Lines Awards includes the following sections:

1. *Abstract (up to 3000 characters in Part A)*

State the goals of the proposal. Summarize the overall plans of the proposed research and how they will meet the stated objectives of the RFA. Describe the rationale for these studies and techniques employed to pursue these goals. If applicable, explain why this proposal cannot be or is not likely to be funded by the federal government.

2. *Public Abstract (up to 3000 characters in Part A)*

   Briefly describe in lay language the proposed research and how it will, directly or indirectly, contribute to the development of diagnostics, tools or therapies. This Public Abstract will become public information; therefore, do not include proprietary or confidential information or information that could identify the candidate and applicant institution.

3. *Statement of Benefit to California (up to 3000 characters in Part A)*

   Describe in a few sentences how the proposed research will benefit the state of California and its citizens. This Statement of Benefit will become public information; therefore, do not include proprietary or confidential information or information that could identify the candidate and applicant institution.

4. *Rationale and Significance (up to 1 page in Part B)*

   Summarize the context and background of the present application and the specific rationale for the work proposed. Evaluate existing knowledge and technology, and specifically identify the gaps that the project is intended to fill. If the aims of the application are achieved, state how this information will make a critical contribution to the stem cell field.

5. *Specific Aims and Timeline (up to 1 page in Part B)*

   Explain the broad, long-term objectives for the derivation and use of the new pluripotent human stem cell lines, e.g. to test a stated hypothesis, solve a specific problem, provide proof of concept for a paradigm, address a critical barrier to progress in the field, or develop new technology. Identify and enumerate each specific aim of the proposal in a concise and step-wise fashion, and provide a realistic time table for completing each proposed specific aim. Where appropriate, provide specific milestones for evaluating progress toward achieving each specific aim.

6. *Research Design and Methods (up to 3 pages in Part B)*

   Describe concisely, but in sufficient detail to permit evaluation of the merit of the research, the experimental design, methods and techniques to be employed to achieve the goals specified in the proposal. Identify the new or risky aspects of the research, anticipated pitfalls, and plans to overcome or circumvent difficulties that may arise. Describe the methods of analysis of results, including criteria for success of the proposed studies and for verification of pluripotency of the newly derived cell lines.

7. *Preliminary Results and Feasibility (up to 2 pages in Part B)*

   Provide preliminary data to support the concepts, hypotheses and/or approaches proposed in the application. Provide any information that will help to establish the experience and competence of the investigator to pursue the proposed project.

8. *References (up to 2 pages in Part B)*

   List all references used in the body of the proposal.

9. *Collaborations and Plans for Sharing New Cell Lines (up to 1 page in Part B)*

   If collaboration is integral to the success of the project, describe how this will be achieved. Provide detailed plans for sharing the new pluripotent cell lines derived with CIRM support with other scientists in the research community (see RFA section XI.C)

10. *Laboratory Facilities including Major Equipment (up to 1 page in Part B)*

    Provide a short description of the facilities and environment in which the work will be done, and the major equipment and resources available for conducting the proposed research. Discuss ways in which the proposed studies will benefit from unique features of the scientific environment or employ useful collaborative arrangements where applicable.

11. *Key Personnel (included in Part A and C)*

    List all key personnel and their roles on the project. Key personnel are defined as individuals who contribute to the scientific

development or execution of the project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. Key personnel may include any technical staff, trainees, co-investigators (collaborators), or consultants who meet this definition. A minimum of one percent effort is required for each key person, except the PI who has a minimum requirement of 10%. For each key personnel (except for technical staff and students) listed, provide a 2 page biographical sketch using the template provided. The sketch should highlight prior research experience and/or special skills related to the proposed research. Include relevant publications.

12. *Budget (included in Part A)*

Provide all budget information requested in the budget section of the Application Information Form. All allowable costs for research grants are detailed in the CIRM Grants Administration Policy (GAP, see section XI.A of this RFA). Under this RFA, allowable costs include the following:

• Salaries for Key Personnel

Salaries for Key Personnel may include the Principal Investigator, Co-Investigators, Research Associates, and technical support staff (all of whom must work in California) based on percent of full time effort commensurate with the established salary structure of the applicant institution. The total salary requested by the PI must be based on a full-time, 12-month staff appointment. Institutions may request stipend, health insurance and allowable tuition and fees as costs for trainees. Administrative support salaries are expected to be covered exclusively by allowed Indirect Costs.

• Supplies

Grant funds will support supplies, including specialized reagents, reimbursement costs for human tissue donations (see section XI.D of this RFA for details), and animal costs. Minor equipment purchases (< $5,000 per item) are considered Supplies and may be included as direct costs in the budget.

• Travel

Recipients (PIs) of CIRM New Cell Lines Awards are required to attend an annual CIRM-organized meeting in California and should include in the budget the travel costs for this meeting. Travel costs associated with collaborations necessary to the grant are allowable. Details of allowable travel costs can be found in the CIRM GAP (see section XI.A of this RFA).

• Equipment

Major equipment (> $5,000 per item) necessary for conducting the proposed research at the applicant institution should be itemized. Equipment costs should not be included as allowable direct costs in indirect cost calculations.

• Indirect Costs

Indirect costs will be limited to 20 percent of allowable direct research funding costs awarded by CIRM (i.e., project costs and facilities costs), exclusive of the costs of equipment, tuition and fees, and subcontract amounts in excess of $25,000.

VII. Submitting an Application

Applications will only be accepted from PIs who 1) have been officially nominated on a CNF by their host institution and 2) have submitted a Letter of Intent (LOI) that was accepted by CIRM.

The application for CIRM New Cell Lines Awards consists of three parts:

Part A: Application Information Form

Part B: New Cell Lines Award Research Proposal

Part C: Biographical Sketches for Key Personnel

All three parts of the application for CIRM New Cell Lines Awards (see section VI.C of this RFA) must be submitted together and received by CIRM no later than **5:00PM (PST) on February 5, 2008, in both electronic form as well as in hard copy (signed original and five copies)**. **No exceptions will be made.**

Candidates must use the appropriate CIRM templates to complete Parts A, B and C. These templates will be available on the CIRM website by December 17, 2007. Send electronic copies of all three parts of the application as attachments in a single email to NewCellLinesAwards@cirm.ca.gov. In addition to the electronic submittal, candidates must submit an original copy of the application (consisting of Parts A-C) signed by both the PI and the institution's Authorized Organizational Official (AOO), plus 5 copies of the full application (preferably double-sided) to:

New Cell Lines Award Application

California Institute for Regenerative Medicine

210 King Street

San Francisco, CA 94107

The electronic version of the application, as well as the original signed application plus the five copies must be received by CIRM no later than 5:00PM (PST) on February 5, 2008. No exceptions will be made.

VIII. Schedule of Receipt and Anticipated Review

Receipt of Candidate Nomination	**5:00PM (PST) on January 10, 2008**
Forms and Letters of Intent:	
Receipt of Applications:	**5:00PM (PST) on February 5, 2008**
Anticipated Review of Applications	**March / April, 2008**
by Grants Working Group (GWG):	
Anticipated Review and Approval by	**June, 2008**
ICOC:	
Earliest Funding of Awards:	**August, 2008**

IX. Review and Award process

CIRM New Cell Lines Award applications will be reviewed by the CIRM Scientific and Medical Research Funding Working Group (the Grants Working Group, or GWG). The GWG consists of fifteen basic and clinical scientists from institutions outside California, seven patient advocates who are members of the Independent Citizen's Oversight Committee (ICOC), and the Chair of the ICOC. The membership of the GWG can be found on the Grants Working Group page. The ICOC was established by the California Stem Cell Research and Cures Act

(Proposition 71) to oversee CIRM and makes all final funding decisions. The composition of the ICOC can be viewed on the ICOC page.

Fifteen scientists on the GWG will review the applications and rate them according to scientific and technical merit. For New Cell Lines Award applications, particular emphasis will be placed on the innovation and the potential for advancing the stem cell field.

The full membership of the GWG will then review the entire portfolio of applications, taking into consideration the following criteria:

- Appropriate balance between innovation and feasibility.
- Appropriate balance between cell lines useful for fundamental research, therapy development, and clinical utility.
- Where relevant, the appropriate balance and range of diseases and genetic diversity addressed
- Other considerations from the perspective of patient advocates.

The GWG's final recommendations for funding will then be forwarded to the ICOC, which will make all final funding decisions.

X. Contacts

For review information:

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For information about electronic forms:

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For programmatic information:

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XI. Other Requirements

A. CIRM Grants Administration Policy

CIRM's Grants Administration Policy (GAP) for Academic and Non- Profit Institutions (Non-Profit GAP) and the Interim GAP for For-Profit Institutions (For-Profit GAP) serve as the standard terms and conditions of grant awards issued by CIRM. All research conducted under this award must comply with the stated policy. The Non-Profit GAP can be found on the Regulations page. CIRM intends to make the Interim For-Profit GAP available by December 19, 2007, subject to approval by the ICOC. Funding from year to year will depend on scientific progress achieved.

B. Intellectual Property Regulations

CIRM has adopted regulations governing intellectual property resulting from CIRM-funded research at Non-Profit and academic institutions (Title 17, California Code of Regulations, sections 100300-100310). This policy can be viewed on our Regulations page.

For-Profit organizations will be regulated by an intellectual property policy as adopted by the ICOC prior to final approval of applications under this RFA.

C. Sharing of New Cell Lines

Newly generated, high quality cell lines have the potential to be utilized in a wide range of applications from fundamental research to drug discovery and diverse clinical uses. To ensure greatest possible impact of this initiative on the advancement of stem cell research and medical therapies, and in compliance with Title 17, California Code of Regulations, section 100304 (available here), CIRM requires that immediately after publication, the new cell lines be made available to other researchers in California for research purposes at no cost or at the actual cost of providing the material. Sharing of new cell lines with researchers outside of California is strongly encouraged. Furthermore, to facilitate access to cell lines generated under this RFA, CIRM requires that they be deposited in a CIRM-sponsored stem cell bank, when such an institution(s) is created in the future. For-Profit organizations will be regulated by an intellectual property policy as adopted by the ICOC prior to final approval of applications under this RFA.

D. Human Stem Cell and Tissue Research Regulations

CIRM has adopted medical and ethical standards for human stem cell research (Title 17, California Code of Regulations, sections 100010 -100110). All research conducted under this award will be expected to comply with these standards which can be viewed at on our Regulations page. While these regulations prohibit donors of gametes, embryos, somatic cells or human tissue from receiving valuable consideration for their donation, they do allow for reimbursement for permissible expenses as determined by an Institutional Review Board (IRB) (Title 17, California Code of Regulations, section 100080). For research activities proposing to obtain gametes, embryos, somatic cells or tissue from human subjects, CIRM requires the candidate to submit, at the time of application, their reimbursement policy describing how they intend to calculate permissible expenses.

Adult stem cells are derived from various differentiated tissues, including human fetal tissue. The use of human fetal tissue in research by CIRM grantees is regulated by Title 17, California Code of Regulations, section 100085.

ICOC approval:
Jun 27, 2008
